

# The Evolution of Central Venous-to-arterial Carbon Dioxide Difference (PCO<sub>2</sub> Gap) during Resuscitation Affects ICU Outcomes: A Prospective Observational Study

Kapil G Zirpe<sup>1</sup>, Anand M Tiwari<sup>2</sup>, Atul P Kulkarni<sup>3</sup>, Hrishikesh S Vaidya<sup>4</sup>, Sushma K Gurav<sup>5</sup>, Abhijit M Deshmukh<sup>6</sup>, Prasad B Suryawanshi<sup>7</sup>, Upendrakumar S Kapse<sup>8</sup>, Abhaya P Bhojar<sup>9</sup>, Piyush A Dhawad<sup>10</sup>, Shameek Mukherjee<sup>11</sup>

Received on: 12 December 2023; Accepted on: 19 January 2024; Published on: 30 March 2024

## ABSTRACT

**Introduction:** The usual methods of perfusion assessment in patients with shock, such as capillary refill time, skin mottling, and serial serum lactate measurements have many limitations. Venous-arterial difference in the partial pressure of carbon dioxide (PCO<sub>2</sub> gap) is advocated being more reliable. We evaluated serial change in PCO<sub>2</sub> gap during resuscitation in circulatory shock and its effect on ICU outcomes.

**Materials and methods:** This prospective observational study included 110 adults with circulatory shock. Patients were resuscitated as per current standards of care. We recorded invasive arterial pressure, urine output, cardiac index (CI), PCO<sub>2</sub> gap at ICU admission at 6, 12, and 24 hours, and various patient outcomes.

**Results:** Significant decrease in PCO<sub>2</sub> gap was observed at 6 h and was accompanied by improvement in serum lactate, mean arterial pressure, CI and urine output in ( $n = 61$ ). We compared these patients with those in whom this decrease did not occur ( $n = 49$ ). Mortality and ICU LOS was significantly lower in patients with low PCO<sub>2</sub> gap, while more patients with high PCO<sub>2</sub> gap required RRT.

**Conclusion:** We found that a persistently high PCO<sub>2</sub> gap at 6 and 12 h following resuscitation in patients with shock of various etiologies, was associated with increased mortality, need for RRT and increased ICU LOS. High PCO<sub>2</sub> gap had a moderate discriminative ability to predict mortality.

**Keywords:** Cardiac index, Circulatory shock, Hemodynamic resuscitation, PCO<sub>2</sub> gap, Serum lactate.

*Indian Journal of Critical Care Medicine* (2024): 10.5005/jp-journals-10071-24680

## HIGHLIGHTS

- Patients with all types of circulatory shock rather than only septic shock, were included.
- Improvement in PCO<sub>2</sub> gap was associated with improved markers of global perfusion and cardiac output.
- Persistently high PCO<sub>2</sub> gap (>6 mm Hg) was associated with poor outcomes.

## INTRODUCTION

Circulatory shock, characterized by inadequate tissue perfusion due to diminished cardiac output affects around a third of ICU patients.<sup>1</sup> Conventional monitoring during resuscitation involves the measurement of mean arterial pressure (MAP), cardiac index (CI), serum lactate levels and urine output (UO).<sup>2</sup> "Normal" MAP does not guarantee adequate tissue oxygenation. With most monitors, CI measurement is limited by invasiveness, non-availability of technical expertise, intermittent nature, inaccuracies due to limitations of algorithms employed. More importantly, it does not reflect microcirculatory or oxygenation status. Hourly UO may be helpful, but is influenced by many other factors, such as pre-morbid renal function. Serum lactate concentration reflects the balance between production and clearance, and the delay in metabolism may reduce its value as a real-time marker. Other mechanisms of lactate production, when present, can give false-positive values.<sup>3</sup> Carbon dioxide easily diffuses out of ischemic tissues to the venous system, making it a more reliable and accurate indicator of hypoperfusion.<sup>4,5</sup>

<sup>1,2,4-11</sup>Neurotrauma Intensive Care Unit, Ruby Hall Clinic, Pune, Maharashtra, India

<sup>3</sup>Department of Anaesthesia and Critical Care, Tata Memorial Hospital, Mumbai, Maharashtra, India

**Corresponding Author:** Anand M Tiwari, Neurotrauma Intensive Care Unit, Ruby Hall Clinic, Pune, Maharashtra, India, Phone: +91 7798255626, e-mail: dranandtiwari@gmail.com

**How to cite this article:** Zirpe KG, Tiwari AM, Kulkarni AP, Vaidya HS, Gurav SK, Deshmukh AM, *et al.* The Evolution of Central Venous-to-arterial Carbon Dioxide Difference (PCO<sub>2</sub> Gap) during Resuscitation Affects ICU Outcomes: A Prospective Observational Study. *Indian J Crit Care Med* 2024;28(4):349–354.

**Source of support:** Nil

**Conflict of interest:** Dr. Kapil G Zirpe and Dr. Atul P Kulkarni are associated as the Editorial Board Member of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of these Editorial Board Members and their research group.

PCO<sub>2</sub> gap in health ranges from 2 to 5 mm Hg, and it is the difference between partial pressure of carbon dioxide (CO<sub>2</sub>) in mixed venous blood (PvCO<sub>2</sub>) and arterial blood (PaCO<sub>2</sub>).<sup>6</sup> A higher PCO<sub>2</sub> gap (>6 mm Hg) identifies inadequacy of cardiac output for sufficient tissue perfusion, and need for further resuscitation.<sup>7</sup> We therefore hypothesized that persistently high PCO<sub>2</sub> gap during resuscitation in patients with shock, will allow identification of patients with poor outcomes. Objectives of the current study

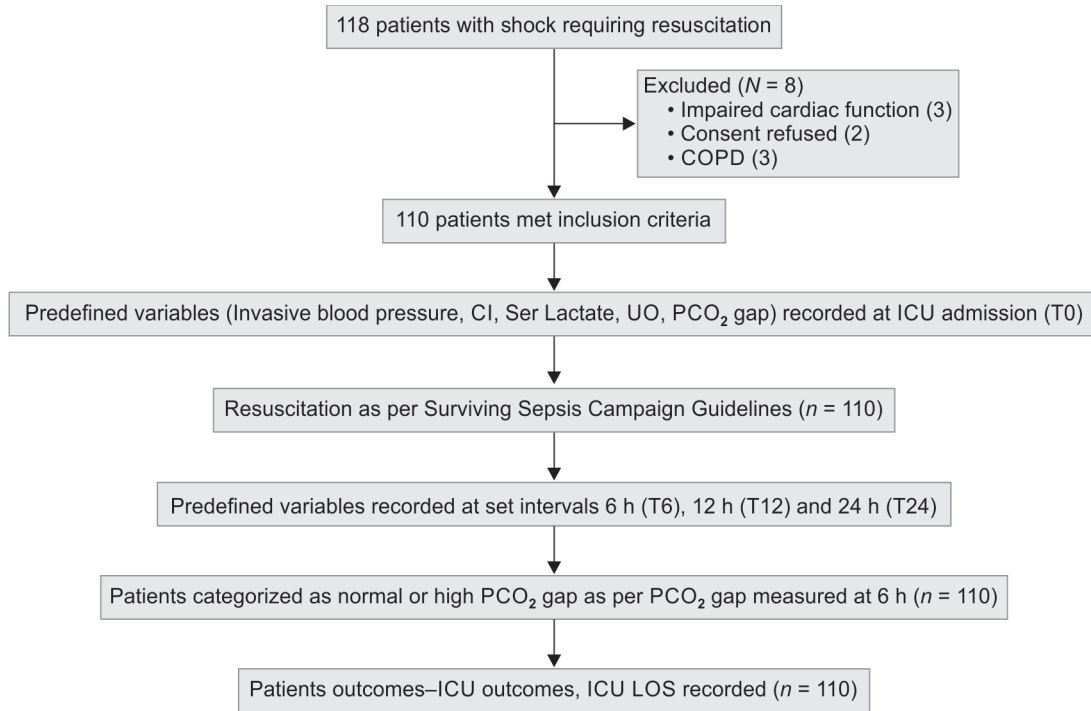


Fig. 1: Patient flow in study

were to evaluate serial change in PCO<sub>2</sub> gap during resuscitation in circulatory shock, and its effect on ICU outcomes.

## MATERIALS AND METHODS

This single-center, prospective observational study was conducted in the ICU of a high-volume tertiary care hospital in Western India, after obtaining Institutional Ethical committee (EC/NEW/INST/2020/736) clearance and registration with Clinical Trial Registry of India (CTRI/2022/09/045990). We followed the principles of the Helsinki declaration. We screened 118 adults with shock (systolic blood pressure <90 mm Hg or MAP <65 mm Hg) who needed resuscitation for inclusion over 20 months (July 2021 to February 2023). Consent was sought in all screened patients.

We included 110 adults (age > 18 y) with shock. Pregnant patients, and those with impaired cardiac function (EF <40%) or chronic obstructive pulmonary disease, chronic kidney disease and those who refused consent were excluded (Fig. 1).

Demographic data (age, gender, comorbid conditions, APACHEII, GCS) and type of shock were recorded. A central venous catheter in the internal jugular vein and arterial cannula in either radial or femoral artery were placed in all patients. All patients were resuscitated as per the surviving sepsis campaign guidelines.<sup>8</sup>

Time of collecting the first pair of samples for calculating the PCO<sub>2</sub> gap (difference in PCO<sub>2</sub> in blood from central venous and artery blood gas samples) was designated as time 0 hours (T0). At this time and subsequent specified intervals, a predefined set of variables were recorded: SBP, diastolic blood pressure (DBP) and MAP, arterial lactate, CI (using 2 D echocardiography). The specified intervals were as follows: 6, 12, and 24 h and designated T6, T12, and T24. Need for vasopressors, mechanical ventilation, and renal replacement therapy (RRT) were also recorded. ICU length of stay (ICU LOS) and outcome were noted. Subsequent therapy of all patients, after 24 h, was as per the discretion of the attending staff. Prior research regarded a PCO<sub>2</sub> gap ≥6 mm Hg as abnormal.<sup>7,9</sup>

The enrolled patients automatically got divided in two groups after 6 h of resuscitation (T6), as per PCO<sub>2</sub> measurement (with 6 mm Hg as the cut-off). The two groups were labelled low PCO<sub>2</sub> group (PCO<sub>2</sub> ≤6 mm Hg) and high PCO<sub>2</sub> group (PCO<sub>2</sub> >6 mm Hg), respectively.

The primary outcome was ICU mortality, and the secondary outcomes were ICU LOS, need for RRT, ability of PCO<sub>2</sub> gap to predict ICU mortality measured at 6 and 12 h.

Sample size calculation and statistics: The sample size was determined using the following formula.<sup>10</sup>

$$[n = z^2 p(1-p)/d^2].$$

Here, the proportion (p) was taken as 42.5% from a previously published study.<sup>11</sup> Z-value at 95% confidence interval, with d as 10% margin of error. The estimated sample size was 94 and we decided finally to enroll 110 patients, with presumed loss of 15% data due to drop-outs or missing values.

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as relative frequency and percentage. Independent Student's *t*-test was used for normally distributed (parametric) continuous variables. The Mann–Whitney *U* test was used for skewed (non-parametric) continuous variables. Chi-square test was used to compare categorical variables. Receiver operating characteristic curve (ROC curve) was drawn for PCO<sub>2</sub> gap at different time points to identify to predicted mortality. A "p-value" < 0.05 was considered as statistically significant. Statistical analysis was done using an online statistical calculator.<sup>12</sup>

## RESULTS

We screened 118 adults who presented with shock over a period of 20 months and enrolled 110 patients (Fig. 1). The demographics, comorbidities, and baseline variables of study population at admission to ICU are depicted in Table 1. Nearly, 43.6% (n = 48)

**Table 1:** Demographics, comorbidities and base line variables

Patient characteristics	Total (n = 110)
Age (years) median (IQR)	56 (43–67)
Male n (%), female n (%)	72 (65.5%), 38 (34.5%)
Comorbid illness	48 (43.6%)
Diabetes mellitus (DM)	18 (16.4)
Hypertension (HT)	17 (15.5)
Hypothyroidism	7 (6.4)
Malignancy	2 (1.8)
>1 comorbidity	4 (3.6)
None	62 (56.4)
Type of shock*	
Distributive	44 (40)
Hypovolemic	40 (36.4)
Neurogenic	10 (9)
Combined etiology	16 (14.5)
Clinical variables median (IQR)	
APACHE II score	15 (12–20)
GCS score	9 (6–14)
Required vasopressor support	105 (95.5)
Required ventilation	65 (59)
Required renal replacement therapy (RRT)	10 (9)
Hemodynamic variables, (mean ± SD)	
Systolic blood pressure (SBP) mm Hg	71.5 ± 7.6
Diastolic blood pressure (DBP) mm Hg	47.5 ± 6.3
Mean arterial pressure (MAP) mm Hg	55.5 ± 5.7
Heart rate (HR) beats/min	108 ± 7
Urine output (UO) mL/h	32 ± 5.4
Laboratory/diagnostic variables (mean ± SD)	
PCO <sub>2</sub> gap (mm Hg)	10 ± 3.7
Serum lactate (mmol/L)	3.9 ± 2.7
pH	7.26 ± 0.12
(Echocardiographic) cardiac index L/min/m <sup>2</sup>	2.8 ± 0.5

\*(Type of shock) as decided by clinician

of the patients had comorbidities and most patients had either distributive or hypovolemic shock. The mean (± SD) MAP was 55.5 ± 5.7 mm Hg, and 96% of the patients needed vasopressor therapy.

Figure 2 shows the changes in the variables of interest over the entire study period at the predefined intervals in the whole patient cohort. All the variables showed a steady improvement over 24 h (decline in PCO<sub>2</sub> gap, serum lactate levels and an increase in the CI and UO). However, only the initial decrease in the PCO<sub>2</sub> gap and increase in UO (from 0 to 6 h) was statistically significant.

The patients then were divided in two groups as per the level of PCO<sub>2</sub> gap at 6 h, that is, those with low (≤6 mm Hg) and high PCO<sub>2</sub> gap (> 6 mm Hg). We compared the values of the other predefined variables (PCO<sub>2</sub>, serum lactate, UO and CI) between these two groups (Fig. 3).

A significant decrease in PCO<sub>2</sub> was seen patients with low PCO<sub>2</sub> group over the course of next 18 h ( $p < 0.05$ ), while the PCO<sub>2</sub> gap steadily increased over this period in high PCO<sub>2</sub> gap group.

The mean CI in the low PCO<sub>2</sub> group increased significantly ( $p < 0.05$ ) during the first 6 h, while the change was minimal between 6 and 12 h and it increased significantly ( $p < 0.05$ ) in the next 12 h. Contrary to this, the CI decreased in the over the next 18

h in the high PCO<sub>2</sub> group. Serum lactate steadily and significantly declined in the low PCO<sub>2</sub> group from T0, at T6 and T12 ( $p < 0.05$ ), while it increased in the over the next 18 h in high PCO<sub>2</sub> group. Urine output improved over the entire study period in the low PCO<sub>2</sub> group, but reduced in the same period in the High PCO<sub>2</sub> group (Fig. 3).

Of 110 patients, 29 (26.3%) died, of which 26 (89.6%) were from the high PCO<sub>2</sub> group while it was three (10.3%),  $p = 0.001$  were from low PCO<sub>2</sub> group.

The median (IQR) ICU LOS was significantly longer [6 (4–10) vs 5 (3–7) d,  $p = 0.002$ ] in patients with high PCO<sub>2</sub> gap group. Nine (15%) patients in high PCO<sub>2</sub> group and one (2%) patient in low PCO<sub>2</sub> group required RRT during their ICU stay ( $p = 0.08$ ).

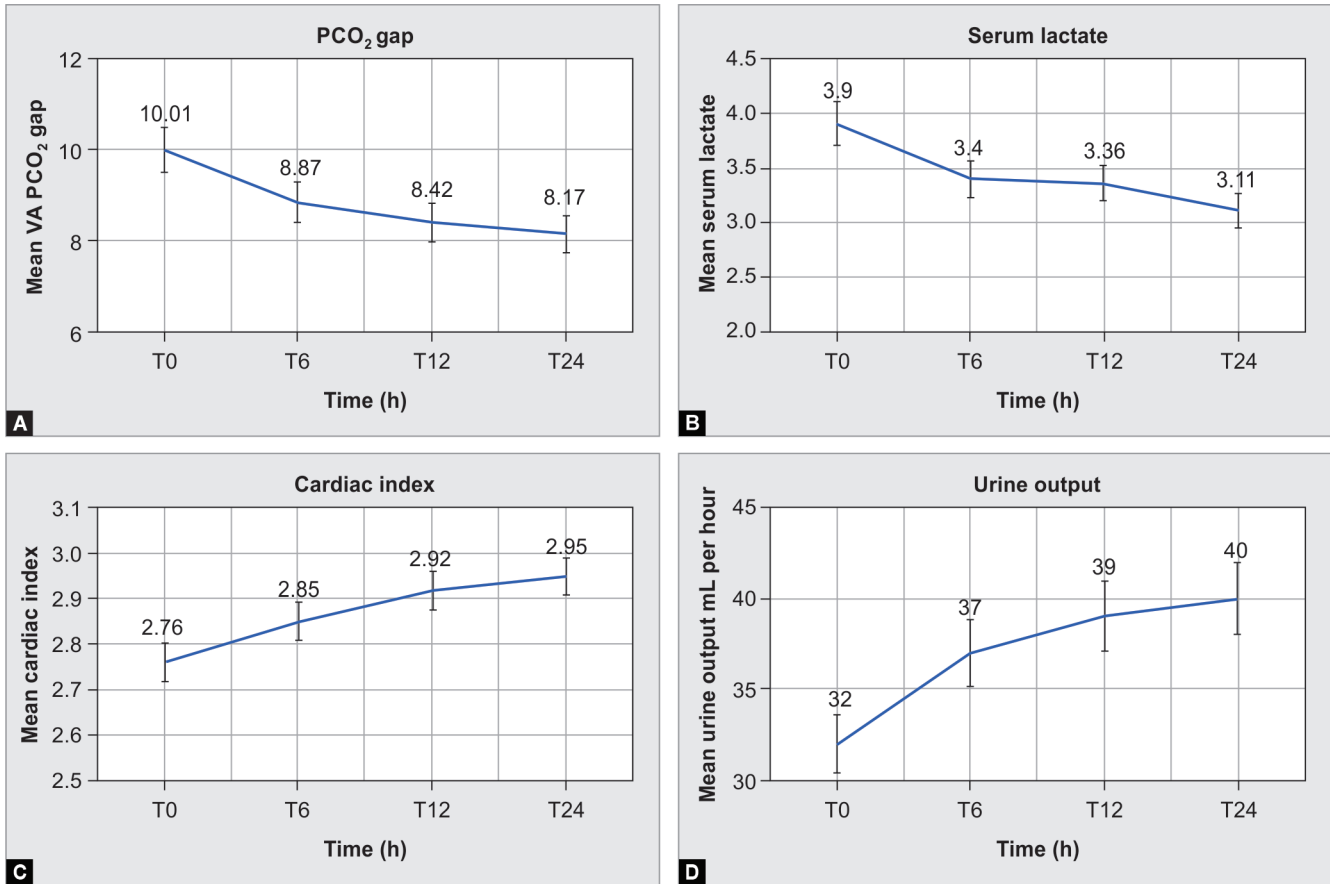
The AUROC of PCO<sub>2</sub> gap at both 6 h (0.775) and 12 h (0.771) showed moderate ability to discriminate between survivors and non-survivors (Fig. 4).

## DISCUSSION

In this prospective observational study, we found that patients in whom the PCO<sub>2</sub> gap decreased following resuscitation at 6 h had improved survival, reduced ICU LOS and need for RRT. The PCO<sub>2</sub> gap is determined by calculating the difference between venous and arterial partial pressures of CO<sub>2</sub>. Ideally a mixed venous blood sample should be used to obtain the venous PCO<sub>2</sub>, which is difficult, since pulmonary artery catheters are rarely used nowadays. Since there is good agreement between central and mixed venous PCO<sub>2</sub> readings, we can use central venous PCO<sub>2</sub>, in place of mixed venous PCO<sub>2</sub>.<sup>13</sup> The current study endeavors to illustrate the role of timing of PCO<sub>2</sub> gap measurements, integrated with commonly used variables of perfusion (serum lactate, CI, and urine output). We observed a significant decline in the PCO<sub>2</sub> gap associated with a concurrent decline in serum lactate, an increase in urine output, and an increase in CI at time intervals of T6, T12, and T24, while a contrasting effect was observed in those with persistently high PCO<sub>2</sub> gaps. Many studies evaluating the PCO<sub>2</sub> gap in clinical situations employed a cut-off value of 6 mm Hg, above which the gap is regarded excessively elevated.<sup>14–16</sup> High PCO<sub>2</sub> gap (>6 mm Hg) is a sensitive indicator of inadequate blood flow to the tissues.<sup>5</sup> In our cohort of patients with shock (mean [± SD] MAP = 55.5 ± 5.7 mm Hg) with the mean PCO<sub>2</sub> gap was (10 ± 3.7) mm of hg high at the time of admission to ICU (T0). PCO<sub>2</sub> gap seems to be a better tool than the traditional markers such as serum lactate and UO for assessing the efficacy of fluid resuscitation.<sup>3,17</sup> Elevation of serum lactate probably occurs in the later stages of hypoperfusion and seems to be a less sensitive parameter of hypoperfusion.<sup>18</sup>

There was no correlation between PCO<sub>2</sub> gap and serum lactate at admission to the ICU [Spearman's rank correlation coefficient ( $rs$ ) = 0.16,  $p = -0.08$ ]; however, a significant correlation was observed at later time intervals [T6 ( $rs = 0.5$ ,  $p < 0.0001$ ), T12 ( $rs = 0.6$ ,  $p < 0.001$ )] and T24 ( $rs = 0.7$ ,  $p < 0.001$ ). We also observed significant negative correlation between PCO<sub>2</sub> gap and CI at T12 ( $rs = -0.5$ ,  $p < 0.05$ ) and T24 ( $rs = -0.6$ ,  $p < 0.05$ ).

Our results are consistent with the results of a previous study by Mallat et al.<sup>19</sup> They also reported no correlation between PCO<sub>2</sub> gap with serum lactate levels T0, ( $r = 0.13$ ,  $p = 0.25$ ) and a moderate correlation at T6 ( $r = 0.42$ ,  $p = 0.001$ ). They also reported significant correlations between CI with PCO<sub>2</sub> gap (T0:  $r = 0.69$ ,  $p < 0.0001$ ; T6:  $r = 0.54$ ,  $p < 0.0001$ ). Cuschieri et al. also reported a significant inverse relationship between the PCO<sub>2</sub> gap and CI in critically sick patients with shock in their cohort, of which one third of patients had cardiogenic shock.<sup>20</sup>



Figs 2A to D: Changes in variables over 24 hours in entire cohort

In health, the PCO<sub>2</sub> gap ranges between 2 and 5 mm Hg indicating adequacy of venous blood drainage, that is, cardiac output (CO).<sup>21,22</sup> Other studies in critically ill patients have also reported a negative correlation between PCO<sub>2</sub> gap and CI.<sup>22,23</sup>

PCO<sub>2</sub> gap serves as a valuable method for estimating cardiac function. Tsousi GG et al.<sup>24</sup> reported the use of PCO<sub>2</sub> gap as a simple tool for reliably estimating the cardiac performance in neurosurgical patients barring further need for invasive monitoring.

Our study included patients who had shock due to various etiologies, apart from septic shock.

Several studies have demonstrated previously an increased PCO<sub>2</sub> gap during hypovolemic, cardiogenic, obstructive, and septic shock.<sup>25-27</sup>

We found that the patients with persistently high PCO<sub>2</sub> gap for 24 h had increased the need for RRT and had longer ICU LOS, similar to the findings reported by Robin et al.,<sup>28</sup> where high PCO<sub>2</sub> gap (6 mm Hg) was associated with increased organ failure, duration of mechanical ventilation, and a longer hospital stay.

All patient enrolled in the present study had high PCO<sub>2</sub> gap at ICU admission. If the PCO<sub>2</sub> gap remains high persistently, it may indicate low cardiac output and significant microcirculatory dysfunction, leading to an unfavorable outcome. Clinicians should be aware that acute changes in pH or PaCO<sub>2</sub> caused by hyperventilation can affect PCO<sub>2</sub> gap regardless of tissue perfusion. Despite these findings, PCO<sub>2</sub> gap remains a clinically useful diagnostic tool for detecting tissue perfusion derangements.<sup>29,30</sup>

We tried to analyze if high PCO<sub>2</sub> gap is a good discriminator to predict mortality. The AUROC (AUC = 0.76) at T6 and T12 suggests a moderate discriminatory ability.

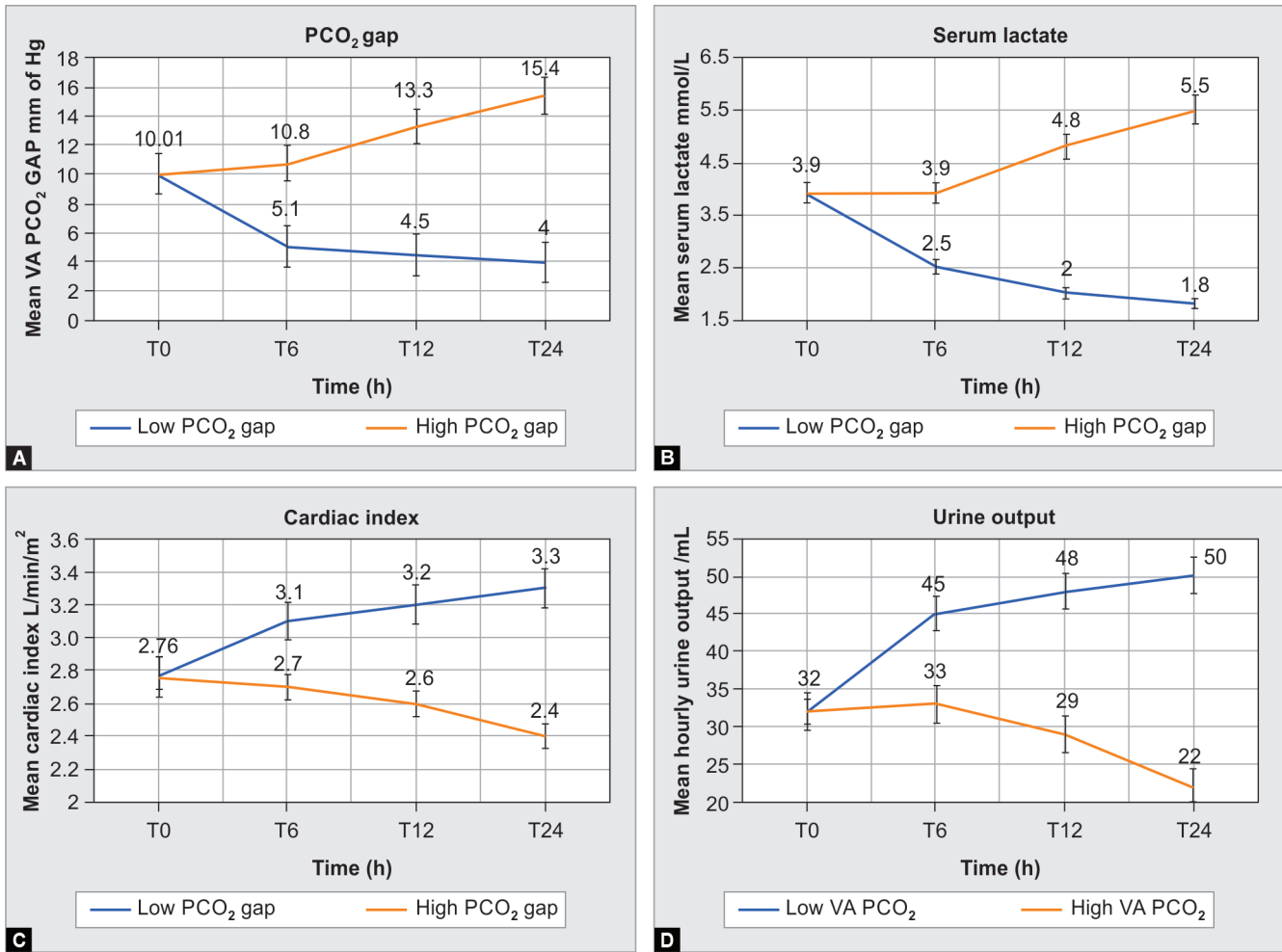
Our study is limited by being single-center, observational, that is, non-interventional, and non-randomized. It is not therefore possible comment on the impact of therapy targeting high PCO<sub>2</sub> gap. Another limitation of our study is the lack of clarity regarding the course of data about treatment received by the patients prior to ICU admission. Strength of current study is a large sample size with circulatory shock of varying etiology.

## CONCLUSION

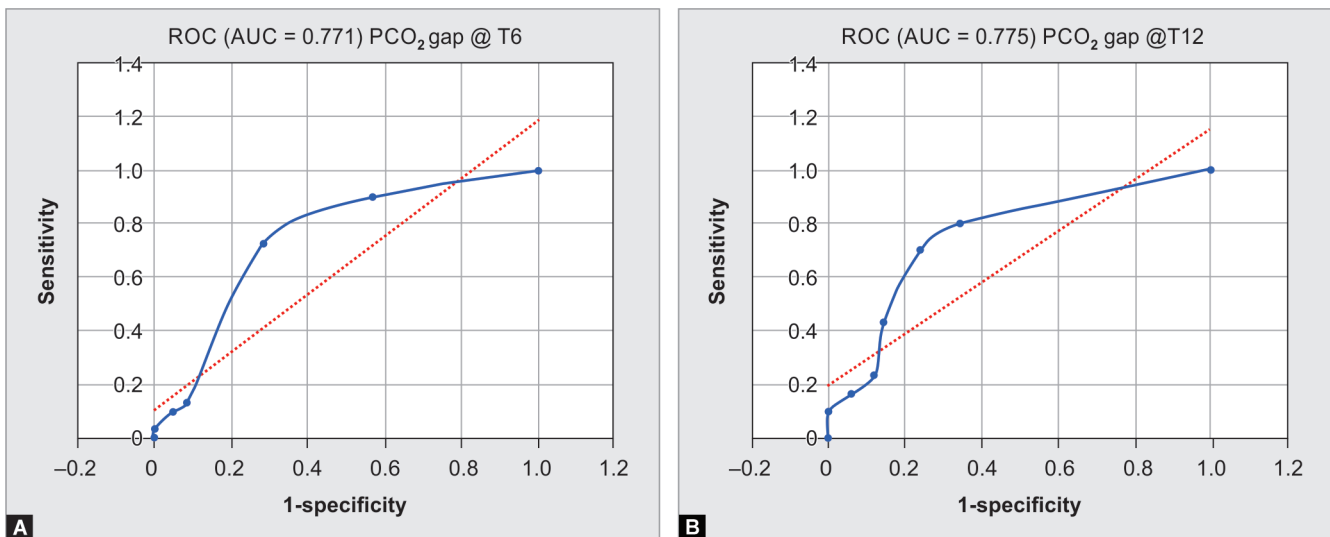
In this prospective observational study, we found that a persistently high PCO<sub>2</sub> gap at 6 and 12 h following resuscitation in patients with shock of various etiologies, was associated with increased mortality, need for RRT and increased ICU LOS. High PCO<sub>2</sub> gap had a moderate discriminative ability to predict mortality.

## AUTHORS' CONTRIBUTION

Kapil G Zirpe and Anand M Tiwari were involved in concept/design, definition of intellectual content, literature search, data acquisition, data analysis, manuscript preparation, manuscript editing, manuscript review guarantor. Atul P Kulkarni carried out concept/design, data analysis, manuscript preparation, manuscript editing, and as a manuscript review guarantor. Hrishikesh S Vaidya,



Figs 3A to D: Comparisons of changes in variables in high vs low PCO<sub>2</sub> groups



Figs 4A and B: ROC curve for PCO<sub>2</sub> gap @ (A) 6 h; (B) 12 h with ICU mortality

Sushma K Gurav, Abhijit M Deshmukh, Prasad B Suryawanshi, Upendrakumar S Kapse, Abhay P Bhojar, Piyush A Dhawad, and Shameek Mukherjee performed the data acquisition and also worked as manuscript review guarantor.

**ORCID**

Kapil G Zirpe <https://orcid.org/0000-0002-8140-727x>  
 Anand M Tiwari <https://orcid.org/0000-0002-9791-8365>



Atul P Kulkarni  <https://orcid.org/0000-0002-5172-7619>  
 Hrishikesh S Vaidya  <https://orcid.org/0000-0002-8015-0898>  
 Sushma K Gurav  <https://orcid.org/0000-0001-6875-2071>  
 Abhijit M Deshmukh  <https://orcid.org/0000-0001-5602-291x>  
 Prasad B Suryawanshi  <https://orcid.org/0000-0001-7306-8434>  
 Upendrakumar S Kapse  <https://orcid.org/0000-0002-5279-4485>  
 Abhaya P Bhoyar  <https://orcid.org/0000-0002-0460-3162>  
 Piyush A Dhawad  <https://orcid.org/0000-0001-7237-3963>  
 Shameek Mukherjee  <https://orcid.org/0009-0004-7471-9453>

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